



(WO/2000/037081) NOVEL FORMULATION

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Abstract: A modified release formulation contains (R)-1-(3-(10,11-Dihydro-5H-dibenzo [a,d]icyclo -hepten-5-ylidene) -1-propyl) -3-piperidinecarboxylic acid or pharmaceutically compound thereof.

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NOVEL FORMULATION FIELD OF INVENTION The present invention relates to a novel formulation containing (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof, and to its use in the treatment and/or prophylaxis of certain disorders.

BACKGROUND OF THE INVENTION WO 95/18793 and WO 97/22336 discloses inter alia (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof, and the use of the compound to treat all painful, hyperalgesic and/or inflammatory conditions in which C-fibres play a pathophysiological role by eliciting neurogenic pain or inflammation. Further, it has been demonstrated that (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof, is useful in reducing blood glucose and/or inhibit the secretion, circulation or effect of insulin antagonizing peptides like CGRP or amylin.

The formulations containing (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof, as suggested in WO 95/18793 and WO 97/22336, relates to formulations which may be prepared by conventional techniques. The formulations mentioned may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

The half-life for (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid is relatively short, and in order to control the release of the compound in such a manner that an effective concentration in the blood can be maintained over an extended period of time but also that the drug concentration in the blood remains relatively constant over an extended period of time, there exists a need for a modified release formulation for (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid.

The use of modified release formulations will furthermore improve patient compliance as it reduces the numbers of dosages per day to be taken.

Thus one object of the invention is to provide modified release formulations containing (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof in order to reduce the fluctuations in plasma concentrations and thereby reduce any inconvenience hereof.

In order to reduce plasma fluctuations it is necessary to provide modified release formulations with zero-order drug release. However, zero-order drug release is difficult to obtain for modified release products, especially for matrix tablets comprising hydroxypropylmethylcellulose, which is an often used polymer within modified release formulations.

SUMMARY OF THE INVENTION It has now surprisingly been found that modified release formulations with zero-order drug release containing (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof dispersed in a polymeric matrix comprising at least one release rate controlling polymer can be provided.

The present invention further provide modified release formulations with zero-order drug release wherein the polymeric matrix comprises a combination of a polyethylene oxide and a hydroxypropylmethylcellulose so that the in vitro dissolution rate is decreased compared to what is obtained with polyethylene oxide as rate controlling polymer.

Furthermore, the present invention relate to modified release formulations comprising a combination of a polyethylene oxide and a hydroxypropylmethylcellulose making the in vitro zero-order dissolution profile independent of pH, indicating that the in vivo absorption also is zero-order and independent of pH.

The requirements of the dissolution profile for the formulation depends on the disorders to be treated and thereby by the ratio between the polymers used. For disorders having a relatively short treatment period, for example during the night, the dissolution rate should be higher than for disorders requiring once daily treatment. The in vitro dissolution profiles can

be modified according to the actual requirement.

The present invention further provides a method of treating conditions or indications related to all painful, hyperalgesic and/or inflammatory conditions in which C-fibres play a patho-physiological role, e.g. neurogenic pain, neurogenic inflammation, migraine, neuropathy, itching and rheumatoid arthritis; urinary incontinence; angiogenesis as well as indications caused by or related to the secretion and circulation of insulin antagonising peptides, e.g. non-insulin-dependent diabetes mellitus (NIDDM) and ageing-associated obesity, by administering an effective and/or a prophylactic amount of a modified release formulation containing (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically compound thereof to a patient in need thereof.

Furthermore, the present invention also provides the use of a modified release formulation containing (R)-1- (3- (10, 11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically compound thereof in the manufacture of a medicament, for treating the above mentioned conditions or indications.

The present invention also provides a pharmaceutical composition for use in the treatment of the above mentioned conditions or indications which comprises a modified release formulation containing (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically compound thereof.

DESCRIPTION OF THE INVENTION Accordingly, the present invention relates to a modified release formulation with zero-order drug release containing (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof dispersed in a polymeric matrix comprising at least one release rate controlling polymer.

Within the present invention (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid may optionally exist as a pharmaceutically acceptable acid addition salt, metal salt or, optionally alkylated, ammonium salt.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate or similar pharmaceutically acceptable inorganic or organic acid addition salts.

Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in *Journal of Pharmaceutical Science*, 66, 2 (1977) which are known to the skilled artisan.

Also included are the hydrates of the above mentioned acid addition salt which the present compound are able to form.

(R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid may be administered in a pharmaceutically acceptable acid addition salt form or where possible as a metal or a lower alkylammonium salt. Such salt forms exhibit approximately the same order of activity as the free base forms.

In a preferred embodiment of the invention (R)-1- (3- (10, 11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid is in the form of the hydrochloride salt.

(R)-1- (3- (10, 11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof may be prepared according to the procedures generally outlined in WO 95/18793 and WO 97/22338.

By modified release is meant any formulation having prolonged, extended or delayed release.

Examples of modified release formulations which are suitable for incorporating (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid are described in Hui, H. W., Robinson, J. R. and Lee, V. H. L., *Design and Fabrication of Oral Controlled Release Drug Delivery Systems*, Controlled Drug Delivery. Fundamentals and Applications, Sec. Ed. edited by J. R. Robinson and V. H. L. Lee 373-432 1987.

The term "release rate controlling polymer" as used herein includes hydrophilic polymers, hydrophobic polymers or mixtures of hydrophilic and/or hydrophobic polymers that are capable of retarding the release of (R)-1- (3- (10,11-Dihydro-5H-

dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl]-3-piperidinecarboxylic acid in vivo when the compound is dispersed in a polymeric matrix formed from the release rate controlling polymers.

Examples of release rate controlling polymers to be used in this invention include hydroxyalkylcellulose, such as hydroxypropylmethylcellulose and hydroxypropylcellulose; polyethylene oxide; alkylcellulose such as ethylcellulose and methylcellulose; carboxymethylcellulose; hydrophilic cellulose derivatives; polyethylene glycol; polyvinylpyrrolidone; cellulose acetate; cellulose acetate butyrate; cellulose acetate phthalate; cellulose acetate trimellitate; polyvinylacetate phthalate; hydroxypropylmethylcellulose phthalate; hydroxypropylmethylcellulose acetate succinate; polyalkyl methacrylate; and polyvinyl acetate. Other suitable hydrophobic polymers include polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac and hydrogenated vegetable oils.

In a preferred embodiment of the invention, the release rate controlling polymers include a hydroxypropylmethylcellulose, a polyethylene oxide, or a combination thereof.

In a particular embodiment of the invention there is provided a release formulation containing a polyethylene oxide.

In another particular embodiment of the invention there is provided a release formulation containing a hydroxypropylmethylcellulose and a polyethylene oxide.

An especially preferred type of hydroxypropylmethylcellulose for use in accordance with the invention is an hydroxypropylmethylcellulose sold under the trademark Methocel (Dow Chemical Co.) or equivalents. Suitable Methocels include the K grades such as Methocel K15M Premium CR, Methocel K100M Premium CR, Methocel K100 Premium LV and Methocel K4M Premium. Other suitable Methocels include the E, F and J grades.

An especially preferred type of polyethylene oxide for use in accordance with the invention is a polyethylene oxide sold under the trademark Sentry Polyox (Union Carbide Corp.) or equivalents. Suitable Polyoxs include the Polyox WSR grades such as Polyox WSR Coagulant, PolyoxWSR-301, PolyoxWSR-303, PolyoxWSR-1105.

The hydroxypropylmethylcelluloses used according to the invention preferably have a viscosity (2 wt% solution at 20 °C) of about 100 to 100,000 cps. Especially suitable are Methocel K types or their equivalents. The polyethylene oxide used according to the invention preferably has a molecular weight of about 100,000 to 7,000,000, more preferably 900,000 to 7,000,000.

To ensure correct release kinetics, the formulation of the present invention contains about 5 and 75% by weight, preferably about 20 and 50% by weight release rate controlling polymer (s).

The modified release formulations according to the present invention may preferably include any relevant filler. The choice of these excipients and their quantity may easily be determined by a person skilled in the art. The excipients includes diluents, various binders, disintegrants, lubricants, colorants, sweeteners and the like.

Suitable diluents include pharmaceutically acceptable inert fillers such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose such as Avicel pH112, Avicel pH101 and Avicel pH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose DGL 21; dibasic calcium phosphate such as Emcompress; mannitol; starch; sorbitol; sucrose and glucose.

Suitable lubricants include, for example, colloidal silicon dioxide such as Aerosil 200; talc; stearic acid; magnesium stearate and calcium stearate.

Suitable binders include polyethylene glycols such as PEG 6000; cetostearyl alcohol; cetyl alcohol; polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene stearates; polyoxamers and waxes.

The modified release formulation can be produced either by using a granulation method followed by compression or by direct compression, thereby avoiding the granulation process step.

Preferred formulations of the modified release formulations are ultimately enteric coated tablets or capsules, wax or polymer coated tablets or capsules or time-release matrices, or combinations thereof. Particular preferred formulations are matrix tablets.

(R)-1- (3- (10, 11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof in the form of a modified release formulation can be used in the treatment of conditions or indications related to all painful, hyperalgesic and/or inflammatory conditions in which C-fibres play a pathophysiological role by eliciting neurogenic pain or inflammation, e. g. acutely painful conditions exemplified by migraine, postoperative pain, burns, bruises, post-herpetic pain (Zoster) and pain as it is generally associated with acute inflammation; chronic, painful and/or inflammatory conditions exemplified by various types of neuropathy (diabetic, post-traumatic, toxic), neuralgia, rheumatoid arthritis, spondylitis, gout, inflammatory bowel disease, prostatitis, cancer pain, chronic headache, coughing, asthma, itching, chronic pancreatitis, inflammatory skin disease including psoriasis and autoimmune dermatoses, osteoporotic pain. The present compound in the form of a modified release formulation may also be used in the treatment of conditions or indications related to urinary incontinence or angiogenesis.

Further, (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof in the form of a modified release formulation can be used in the treatment of conditions or indications caused by or related to the secretion and circulation of insulin antagonising peptides and other peptides derived from the sensory nervous system, e. g. non-insulin-dependent diabetes mellitus (NIDDM) and ageing-associated obesity.

The above mentioned conditions or indications are herein after referred to as the disorders.

The term treatment as used herein may be described as the treatment, prevention, elimination, alleviation or amelioration of one of the above disorders.

The term patient as used herein includes any mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of the above disorders. Such mammals include also animals, both domestic animals, e. g. household pets, and non-domestic animals such as wildlife.

The terms "zero-order drug release" and "first-order drug release" as used herein refer to an in vitro zero-order drug release and an in vitro first-order drug release respectively.

EXAMPLES The following examples illustrate the present invention. However, the examples are not intended to be construed as limiting.

EXAMPLE 1 Hydroxypropylmethylcelluloses, Methocel K4M Premium, Methocel K15M Premium CR and Methocel K100M Premium CR, as Matrix Polymers in (R)-1- (3- (10,11-Dihydro-5H-dibenzo [a,d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid, HCl tablets. Two different levels of matrix polymers has been investigated. Tablet Strength, mg 90 90 Tablet Gross Mass, mg 300 300 (R)-1- (3- (10, 11-Dihydro-5H-98798.7 dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid, hydrochloride, mg Water q. s. q. s. Matrix Polymer, 60(20%) 180(60%) Lactose, anhydrous, mg 136,8 16,8 Magnesium Stearate, mg 1,5 1,5 Talc, mg 3 3 (R)-1- (3- (10, 11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid, hydroxypropylmethylcellulose, and lactose anhydrous are mixed in a high shear mixer and granulated with water. After drying, the granules are mixed with talc and magnesium stearate and compressed into tablets on a tableting machine.

Dissolution tests has been performed according to USP Paddle method (Water, 50 rpm, n=3). Dissolution profiles as shown in Figures 1 a, 1 b and 1 c.

Results: When using the hydroxypropylmethylcelluloses in concentrations of 20 or 60%, first-order dissolution profiles occur.

The dissolution rates decreases as the content of matrix polymer increases.

EXAMPLE 2 The high molecular weight polyethylene oxide, Sentry Polyox WSR 1105, as matrix polymer in (R)-1- (3- (10, 11-Dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid tablets Tablet Strength, mg 60

(30%) 90(30%) Tablet Gross Mass, 300200 (R)-1-(3-(10,11-Dihydro-5H-65, 8 98.7 dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid, hydrochloride, mg Water q. s. q. s. Sentry Polyox WSR 1105, mg 96 (48%) 180 (60%) Lactose, Anhydrous, mg 35.2 16.8 Magnesium Stearate, mg 1 1.5 Talc, mg 2 3 (R)-1-(3-(10,11-Dihydro-5H-65, 8 98.7 dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid, high molecular weight polyethylene oxide, and lactose anhydrous are mixed in a high shear mixer and granulated with water. After drying, the granules are mixed with talc and magnesium stearate and compressed into tablets on a tableting machine.

Dissolution tests has been performed according to USP Paddle method (Water, 50 rpm, n=3). Dissolution profiles as shown in Figure 2: Results: When using high molecular weight polyethylene oxide, Sentry Polyox WSR 1105, in concentrations of 48 or 60%, zero-order dissolution profiles occur.

The dissolution rate decreases as the content of matrix polymer increases.

EXAMPLE 3 Combination of the high molecular weight polyethylene oxide, Sentry Polyox WSR 1105, and the hydroxypropyl methylcellulose, Methocel K100M Premium CR as Matrix Polymers in (R)- 1-(3-(10,11-Dihydro-5H-65, 8 98.7 dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid Tablets. Tablet Strength, mg 60 60 60 Tablet Gross Mass, mg 200 200 200 65,865.8(R)-1-(3-(10,11-Dihydro-5H-65.8 dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid, hydrochloride, mg Water q.s. q.s. q.s. Sentry Polyox WSR 1105, mg 96 (48%) 72 (36%) 48 (24%) | Methocel/Methocel K100M Premium CR, mg 24(12%) 48(24%) 72(36%) Lactose, Anhydrous, mg 11.2 11.2 11.2 Magnesium Stearate, mg 1 1 1 Talc, mg 2 2 2 (R)-1-(3-(10,11-Dihydro-5H-65, 8 98.7 dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid, high molecular weight polyethylene oxide, hydroxypropyl methylcellulose, and lactose anhydrous are mixed in a high shear mixer and granulated with water.

After drying, the granules are mixed with talc and magnesium stearate and compressed into tablets on a tableting machine.

Dissolution tests has been performed according to USP Paddle method (Water, 50 rpm, n=3). Dissolution Profiles as shown in Figure 3.

Results: Although hydroxypropylmethylcellulose as matrix polymers causes first-order dissolution profiles (Example 1), when combining the hydroxypropylmethylcellulose, Methocel K100M Premium CR, and the high molecular weight polyethylene oxide, Sentry Polyox WSR 1105, zero-order dissolution profiles are obtained. Even with 24% high molecular weight polyethylene oxide and 36% hydroxypropylmethylcellulose, zero-order dissolution profiles are obtained.

It is possible to adjust the dissolution rate and dissolution profile by changing the ratio between the amounts of the two matrix polymers.

EXAMPLE 4 Investigation of the dissolution profiles pH-dependence has been performed. Two different formulations has been investigated. One formulation contains Sentry Polyox WSR 1105 as matrix polymer and the other contains both Sentry Polyox WSR 1105 and Methocel K100M Premium CR as matrix polymers. Tablet Strength, mg 30 30 Tablet Gross Mass, mg 200 200 (R)-1-(3-(10, 11-Dihydro-5H-32, 9 32, 9 dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid, hydrochloride, mg Water q. s. q. s. Sentry Polyox WSR 1105, 96(48%) 72(36%) Methocel K100M Premium CR, mg 0 48 (24%) Lactose, Anhydrous, mg 68.1 11.2 Magnesium Stearate, mg 1 1 Talc, mg 2 2 (R)-1-(3-(10,11-Dihydro-5H-65, 8 98.7 dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3- piperidinecarboxylic acid, matrix polymer (s), and lactose anhydrous are mixed in a high shear mixer and granulated with water. After drying, the granules are mixed with talc and magnesium stearate and compressed into tablets on a tableting machine.

Dissolution tests has been performed according to USP Paddle method (50 rpm, n=3) in the following media: Water 0.1 N hydrochloric acid (pH 1) 0.07 M phosphate buffer (pH 4.75) Phosphate-citrate buffer (pH 6.8) Dissolution Profiles for the tablets with Sentry Polyox WSR 1105 as shown in Figure 4a.

Dissolution Profiles for the tablets with Sentry Polyox WSR 1105 and Methocel K100 Premium CR as shown in Figure 4b.

Results: By combining hydroxymethylpropylcellulose, Methocel K100M Premium CR and the high molecular weight polyethylene oxide, Sentry Polyox WSR 1105, zero-order release is obtained independent of pH in the dissolution media.



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CLAIMS 1. A modified release formulation containing (R)-1- (3- (10, 11-Dihydro-5H- dibenzo [asd] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceuti- cally acceptable salt thereof.

2. A formulation according to claim 1 wherein the formulation is a zero-order drug re- lease formulation.

3. A formulation according to any previous claim wherein (R)-1- (3- (10, 11-Dihydro-5H- dibenzo [asd] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid or a pharmaceuti- cally acceptable salt is dispersed in a release rate controlling polymeric matrix comprising at least one release rate controlling polymer.

4. A formulation according to any previous claim, wherein at least one release rate con- trolling polymer is selected from the group consisting of hydroxypropylmethylcellulose, poly- ethylene oxide, or mixtures thereof.

5. A formulation according to any previous claim, wherein at least one release rate con- trolling polymer is selected from the group consisting of hydroxypropylmethylcellulose having a viscosity of about 100 to 100,000 cps, and polyethylene oxide having a molecular weight of about 100,000 to 7,000,000, or mixtures thereof.

6. A formulation according to any previous claim, wherein at least one release rate con- trolling polymer comprises from about 5 to 75% by weight of the formulation.

7. A formulation according to any previous claim, wherein at least one release rate con- trolling polymer comprises from about 20 to 50% by weight of the formulation.

8. A formulation according to any previous claim, wherein (R)-1- (3- (10,11-Dihydro-5H- dibenzo [a, d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid is in the form of the hydrochloride salt.

9. A formulation according to any previous claim which comprises enteric coated tablets or capsules, wax or polymer coated tablets or capsules or time-release matrices, or combinations thereof.

10. A formulation according to claim 9 wherein the formulation is related to matrix tab- lets.

11. A method of treating the disorders by administering an effective amount of a formu- lation according to any previous claim, to a patient in need thereof.

12. A method according to claim 11 wherein the disorders is related to neurogenic inflammation.

13. A method according to claim 11 wherein the disorders is related to non-insulin- dependent diabetes mellitus (NIDDM).

14. Use of a formulation according to any previous claim in the manufacture of a me- dicament for treating the disorders.

15. The use according to claim 14 wherein the disorders is related to neurogenic inflammation.

16. The use according to claim 14 wherein the disorders is related to non-insulin- dependent diabetes mellitus (NIDDM).

17. A process for the preparation of a formulation according to any previous claim, which comprises combining the constituents thereof in the required proportions.